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## **Photodynamic therapy improves skin antisepsis as a prevention strategy in arthroplasty procedures: A pilot study**

Waldmann, Isabelle ; Schmid, Tobias ; Prinz, Julia ; Mühleisen, Beda ; Zbinden, Reinhard ; Imhof, Laurence ; Achermann, Yvonne

**Abstract:** Background: Current standard skin antisepsis to prevent surgical site infections are ineffective to eradicate all skin-colonizing bacteria. Photodynamic therapy (PDT) has shown bactericidal effects in vitro, but no clinical study with improvements in skin antisepsis has been documented. Methods: We investigated the effect of methyl aminolevulinate (MAL)-PDT versus no PDT for skin antisepsis treatment (povidone-iodine/alcohol) in the groin of 10 healthy participants. Skin swabs were taken at baseline, immediately after PDT, and after skin antisepsis treatment to cultivate bacteria. At day 7 and 21, bacterial cultures were repeated before and after antisepsis treatment without PDT. Skin biopsies were performed to examine the grade of inflammation. Results: Skin-colonizing bacteria were found in all 20 participants at baseline sampling. Immediately after MAL-PDT, skin was sterile in 7 (70%) participants before and in all 10 (100%) participants after skin antisepsis treatment. In contrast, we found skin-colonizing bacteria in 5 (50%) participants of the control group receiving only skin antisepsis. After 7 and 21 days, skin sterility was similar to the baseline. We observed slight perivascular inflammation with lymphocytes and eosinophils without changes in the histomorphology of eccrine or sebaceous glands in skin biopsies. PDT was generally well tolerated except for localized redness. Conclusion: MAL-PDT with skin antisepsis treatment sterilized skin immediately after its use but did not maintain sterility 7-21 days post-treatment. Due to local side effects, further clinical studies with less intensive PDT conditions or other photosensitizers are needed before PDT is integrated into clinical practice.

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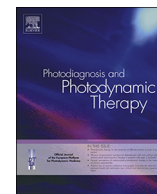


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# Photodynamic therapy improves skin antisepsis as a prevention strategy in arthroplasty procedures: A pilot study

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## ABSTRACT

**Background:** Current standard skin antisepsis to prevent surgical site infections are ineffective to eradicate all skin-colonizing bacteria. Photodynamic therapy (PDT) has shown bactericidal effects in vitro, but no clinical study with improvements in skin antisepsis has been documented.

**Methods:** We investigated the effect of methyl aminolevulinate (MAL)-PDT versus no PDT for skin antisepsis treatment (povidone-iodine/alcohol) in the groin of 10 healthy participants. Skin swabs were taken at baseline, immediately after PDT, and after skin antisepsis treatment to cultivate bacteria. At day 7 and 21, bacterial cultures were repeated before and after antisepsis treatment without PDT. Skin biopsies were performed to examine the grade of inflammation.

**Results:** Skin-colonizing bacteria were found in all 20 participants at baseline sampling. Immediately after MAL-PDT, skin was sterile in 7 (70%) participants before and in all 10 (100%) participants after skin antisepsis treatment. In contrast, we found skin-colonizing bacteria in 5 (50%) participants of the control group receiving only skin antisepsis. After 7 and 21 days, skin sterility was similar to the baseline. We observed slight perivascular inflammation with lymphocytes and eosinophils without changes in the histomorphology of eccrine or sebaceous glands in skin biopsies. PDT was generally well tolerated except for localized redness.

**Conclusion:** MAL-PDT with skin antisepsis treatment sterilized skin immediately after its use but did not maintain sterility 7–21 days post-treatment. Due to local side effects, further clinical studies with less intensive PDT conditions or other photosensitizers are needed before PDT is integrated into clinical practice.

## 1. Introduction

The use of orthopedic implants has been steadily rising over the last decade due to the growing demand for periprosthetic joints in the expanding elderly population. Periprosthetic joint infections (PJI) are one of the most feared complications after surgical intervention as these infections have biofilm etiologies that are difficult to treat and impact the quality of life, increasing health-care costs [1]. Within a mature biofilm, bacteria are protected against most current antibiotics by a coating of exopolysaccharide matrix, preventing antibiotic penetration and by bacterial heterogeneity, decreasing available antibiotic targets within bacteria. The most commonly isolated microorganisms in PJI are staphylococci, streptococci, enterococci, Gram-negative bacteria, and

anaerobic bacteria such as *Cutibacterium acnes*/ *Cutibacterium avidum* (formerly *Propionibacterium acnes*/ *Propionibacterium avidum*) [1,2], all of which may inhabit the normal skin flora.

A majority of PJI are acquired during surgery, with the same bacteria that colonize the skin surface serving as infectious invaders of the orthopedic implant [3]. Skin antisepsis at incision sites should be the primary intervention to prevent commensal bacterial infection into deep tissues during surgery. Recent studies have shown that the current standards for skin antisepsis are not effective enough to sterilize the skin before arthroplasty [4]. Lee et al. showed a significant growth rate of *C. acnes* in 7 out of 10 volunteers with skin biopsies, despite skin preparation with chlorhexidine/alcohol prior to sampling [5]. Maurer et al. detected bacterial growth of skin commensals after standard

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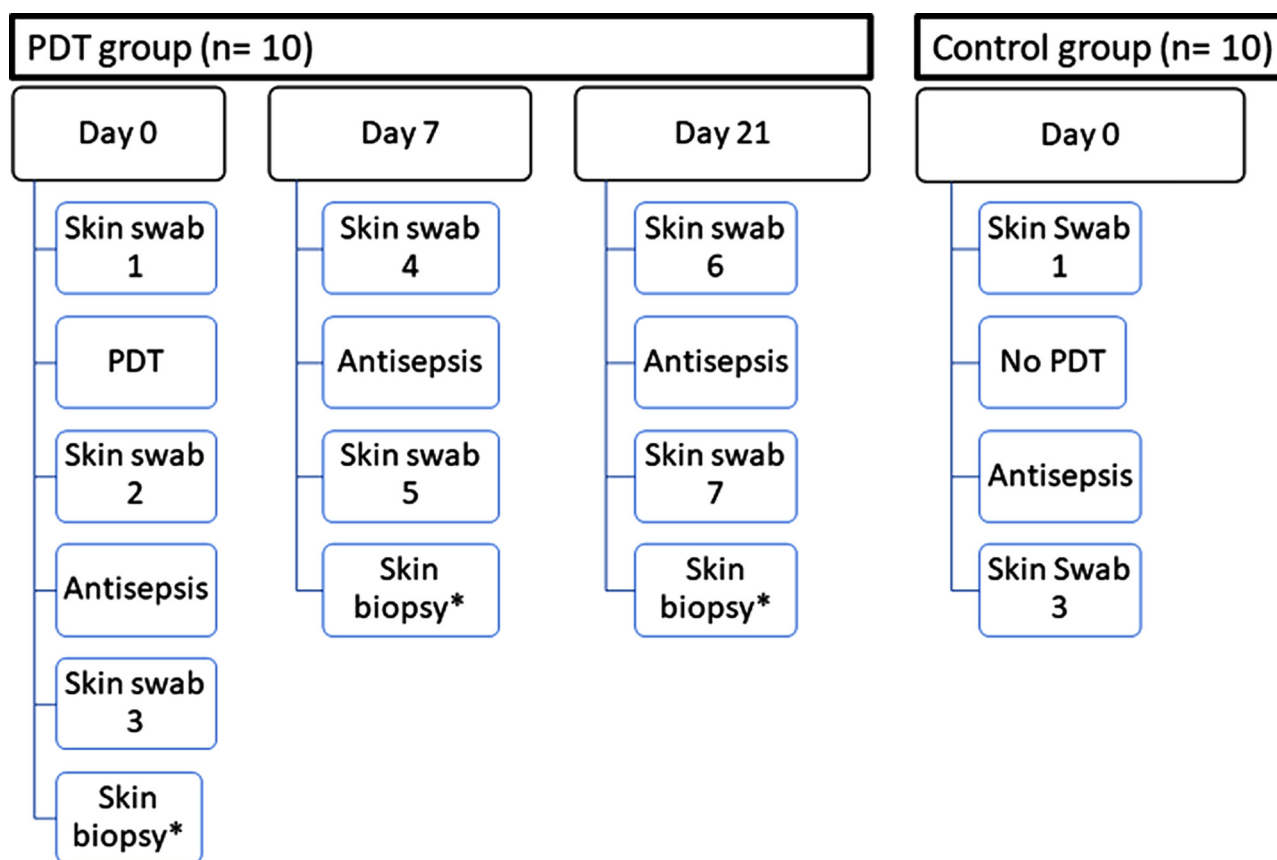


Fig. 1. Study design for 10 participants receiving PDT and 10 control participants.

antisepsis in the groin in 50% of the patients (manuscript in review, oral communication FP 81 at the European Bone and Joint Infection Society (EBJIS) meeting, Antwerp, 2019). Different approaches to improve antisepsis have been examined throughout the years, some with no effects [4] and others with promising results [6,7]. Local antibiotics risk the emergence of bacterial resistance, making this approach undesirable in daily surgical practice [8].

The antimicrobial effect of photodynamic therapy (PDT) has already been established in previous studies and relies on photophysical and photochemical reactions to eliminate bacteria [9,10]. We hypothesize that PDT reduces the growth of skin-colonizing bacteria when combined with skin antisepsis treatment, the latter already being routinely performed prior to arthroplasty surgeries. Therefore, we evaluated the effect of PDT with methyl aminolevulinate (MAL) as the prodrug for the photosensitizer protoporphyrin IX (Pp IX) on skin-colonizing bacteria in a pilot study with 10 healthy participants. Promising results will provide the basis for planning a future clinical study in an orthopedic center. Since PDT triggers subtle skin inflammation which may be suboptimal for immediate surgery, we evaluated the effect of PDT at baseline, immediately after PDT and skin antisepsis treatment, and after 7 and 21 days analyzing bacterial growth and severity of skin inflammation.

## 2. Materials and methods

### 2.1. Participants and study design

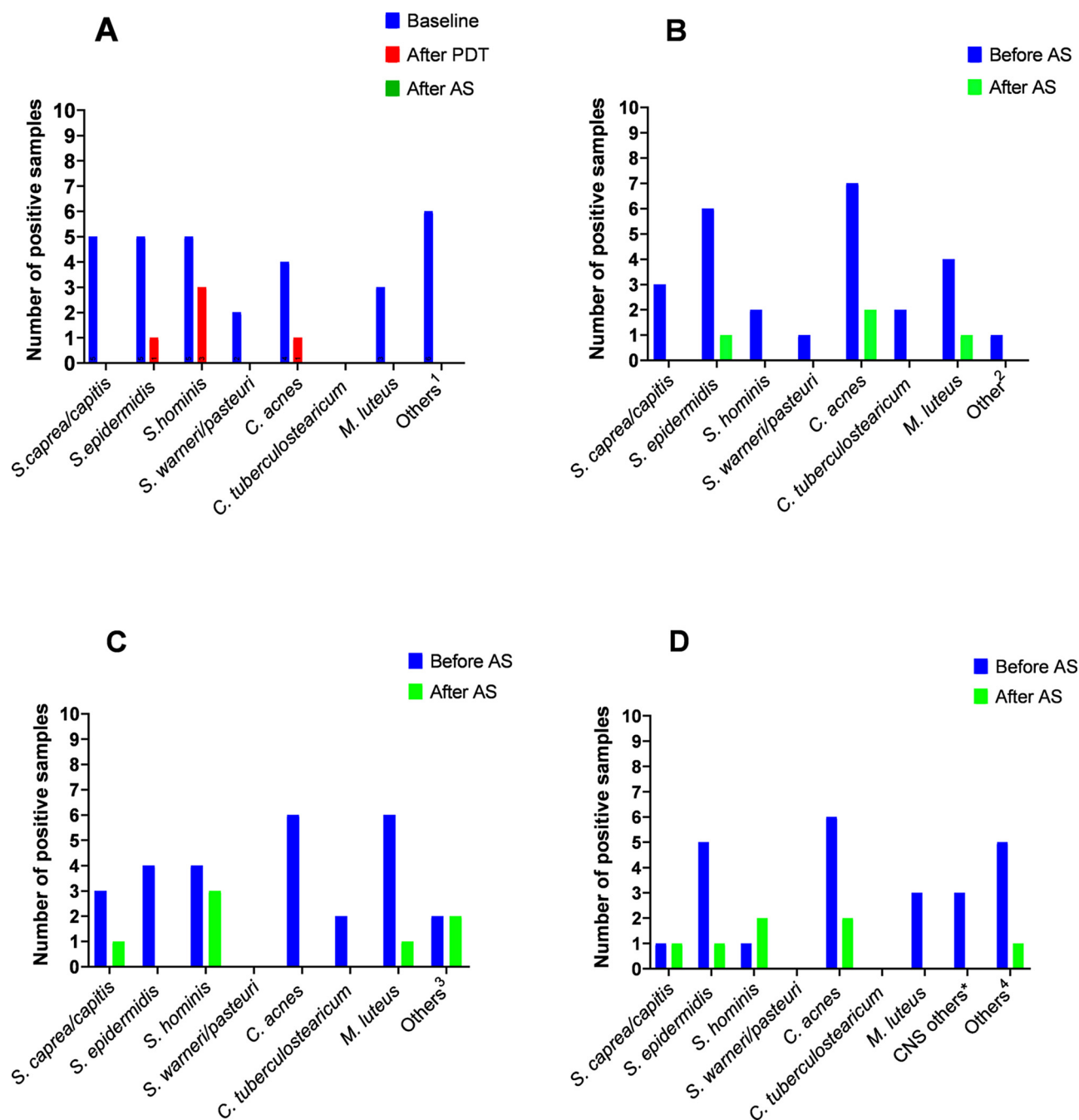
In this single center clinical trial, healthy male and female participants ( $\geq 18$  years) were recruited to have PDT in combination with skin antisepsis. The study was approved by the local ethical committee (BASEC Nr 2019-00252) and an informed consent was obtained from each participant prior to treatment. From September–November 2019,

we enrolled 10 healthy participants for PDT and another 10 healthy participants for the control group to be treated with skin antisepsis only. We excluded pregnant and lactating women, participants unable to follow instructions of the study leaders (e.g. language problems, psychological disorders, dementia, etc), taking antibiotics 14 days prior to PDT or until follow-up at day 14, receiving oral retinoid therapy within the last 6 months or anti-inflammatory agents such as Non-Steroidal Anti-Inflammatory Drugs within 14 days prior and after PDT, taking any photosensitizing drugs within 4 weeks prior to PDT, and those who had a history of photosensitive disorder or Fitzpatrick's skin phototype V–VI.

Participant characteristics such as age, BMI, comorbidities, allergies, and medication were recorded for all 20 participants on the first day of their clinical visit. The study design for both groups is shown in Fig. 1. For all 10 participants receiving PDT treatment, skin swabs were immediately taken before and after PDT and after standard skin antisepsis treatment on days 0, 7, and 21 to investigate the amount of bacterial species on human skin. All study participants had follow-up examinations to evaluate the extent of skin inflammation after PDT. Participants were specifically asked about any redness, pain, skin irritation and itching, other abnormalities, and the need for medications for relief from symptoms. In a subgroup of patients, additional dermis biopsies of the treated groin area were taken immediately after PDT, after 7 days, and again after 21 days. A biopsy from the opposite, untreated side of the body was used as a control.

### 2.2. Skin swabs

Skin swabs were taken from the right groin area, immediately below the anterior superior iliac spine with sterile blades scraping at a 45° angle. Material was removed carefully from the blade and inoculated into an eSwab Collection and Transport System (Copan, Italy). All



**Fig. 2.** Effect of photodynamic therapy (PDT) treatment on specific bacterial species. Panel A: Number of positive samples on day 0 (day of PDT) at baseline (blue), after PDT (red) and after skin antiseptics treatment (AS) (green). Panel B: Number of positive samples 7 days after the PDT before AS (blue) and after AS (green). Panel C: Number of positive samples after 21 days of PDT before AS (blue) and after AS (green). Panel D: Number of positive samples in the control group before AS (blue) and after AS (green).

“Others” included:

Others<sup>1</sup> *Staphylococcus lugdunensis*, *C. avidum*, *Mircococcus flavus*, *Bacillus cereus*, *Anaerococcus sp.*, *Dermobacter hominis*.

Others<sup>2</sup> *Corynebacterium kroppenstedtii*

Others<sup>3</sup> *S. lugdunensis*, *Corynebacterium sp.*, *Corynebacterium aurimucosum*, *Bacillus sp.*

Others<sup>4</sup> *Staphylococcus aureus*, *Corynebacterium sp.*, *Corynebacterium jeikeium*, *D. hominis*

\* *Staphylococcus haemolyticus*, *Staphylococcus saprophyticus*, *Staphylococcus sp.*

swabs were analyzed for bacterial growth at the Institute of Medical Microbiology of the University of Zurich. All skin swabs (1–7) were carried out using the same technique.

### 2.3. Photodynamic therapy (PDT)

PDT requires three elements: a photosensitizer, visible light with a

specific wavelength to excite the photosensitizer, and tissue oxygen. Reactive oxygen species that induce antimicrobial effects by oxidative damage are generated after absorption of a suitable wavelength of light by a photosensitizer in the presence of tissue oxygen [11–13]. MAL is an ester of 5-aminolevulinic acid (5-ALA) which can be found in nearly all bacterial and human cells as a component of the heme biosynthesis pathway. Accumulation of photoactive porphyrins in targeted cells can

**Table 1**

Skin sterility (defined as no viable bacteria using conventional cultures) before and after PDT treatment and following skin antiseptis treatment.

Sterility	Nr/Nr total (%)
<b>Day 0, control group without PDT, n = 10</b>	
Before antiseptis (Skin swab 1)	0/10 (0)
After antiseptis (Skin swab 3)	5/10 (50)
<b>Day 0, PDT treatment, n = 10</b>	
Baseline (Skin swab 1)	0/10 (0)
After PDT (Skin swab 2)	7/10 (70)
After PDT and antiseptis (Skin swab 3)	10/10 (100)
<b>Day 7 after PDT, n = 8</b>	
Before antiseptis (Skin swab 4)	0/8 (0)
After antiseptis (Skin swab 5)	5/8 (62.5)
<b>Day 21 after PDT, n = 10</b>	
Before antiseptis (Skin swab 6)	0/10 (0)
After antiseptis (Skin swab 7)	4/10 (40)

**Table 2**

Histological assessment of skin inflammation.

	Nr/Nr total (%)
<b>Day 0, control group, n = 4</b>	
Perivascular inflammation	0/4 (0)
Inflammation around eccrine sweat glands	0/4 (0)
Inflammation around sebaceous glands	0/4 (0)
<b>Day 0, immediately after PDT, n = 2</b>	
Perivascular inflammation	0/2 (100)
lymphocytes (2/2), eosinophils (1/2), neutrophils (0/2)	
Inflammation around eccrine sweat glands	0/2 (0)
Inflammation around sebaceous glands	0/2 (0)
<b>Day 7, n = 2</b>	
Perivascular inflammation	1/2 (50)
lymphocytes (1/2), eosinophils (1/2), neutrophils (0/2)	
Inflammation around eccrine sweat glands	1/2 (50)
lymphocytes (1/2), eosinophils (1/2), neutrophils (0/2)	
Inflammation around sebaceous glands	0/2 (0)
<b>Day 21, n = 4</b>	
Perivascular inflammation	0/4 (0)
Inflammation around eccrine sweat glands	0/4 (0)
Inflammation around sebaceous glands	0/4 (0)

be achieved by providing it exogenously [9]. Cells with a high metabolic rate such as neoplastic cells and bacteria will accumulate 5-ALA more intensely [14]. 5-ALA has already been used in clinical studies, specifically for PDT treatment of *C. acnes* bacterial biofilms in sebaceous glands [15–18]. Using MAL-PDT in our study, we aimed to reach not only superficial skin-colonizing bacteria, but also eccrine glands acting as a reservoir of bacteria [15,19,20] that are not affected by topical skin antiseptis treatment.

PDT treatment was performed at the Division of Dermatology of the University Hospital of Zurich. MAL (Metvix®, Galderma SA, Tube 2 g) was applied in a sheer layer over the right groin area, covered by a light-impermeable bandage, and allowed to incubate before PDT for 3 h. The area was then exposed to a 633 nm diode (LED; Healite II®; Lutronic; Billerica, MA, USA) for 13 min with an energy dose of 40 J/cm<sup>2</sup>. Photographic documentation of treated skin was made before and after PDT.

#### 2.4. Skin antiseptis with povidone-iodine/alcohol

Antiseptis treatment of the groin was performed 3 times according to standard operation room procedure using Betaseptic (povidone-iodine/alcohol) with at least one-minute interval in between placement.

#### 2.5. Biopsies for dermatohistopathology

In four participants, 4 mm skin punch biopsies of the right groin were taken directly after PDT (n = 2) or one week after PDT (n = 2),

and again after 3 weeks (n = 4). As a control sample, a similar punch biopsy was taken from the left untreated groin in the same participants (n = 4). Skin biopsies were fixed in formalin and embedded in paraffin. Sections were sliced 4 µm thick for hematoxylin and eosin staining and assessed for the presence of inflammation in the perivascular compartment, focusing on areas with eccrine sweat glands and sebaceous glands. In those specimens with inflammation, the type and amount of inflammatory cells (lymphocytes, neutrophils, eosinophils) were assessed.

#### 2.6. Microbiology

Skin swabs were evaluated for any bacterial growth using Columbia sheep blood agar plates without antibiotics (bioMérieux, Mary-l'Etoile, France) and colistin-nalidixic acid blood agar (bioMérieux, Mary-l'Etoile, France) plates for aerobic cultivation. *Brucella* agar plates (in-house sheep blood agar plates with hemin added Vitamin K1 provided by the Institute of Clinical Microbiology, Zurich, Switzerland) were used for anaerobic cultivation with GENbags (bioMérieux, Mary-l'Etoile, France). Cultures were left for at least 7 days at 37 °C to check for persisters. Each suspicious bacterial colony was analyzed for bacterial identification using matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS).

### 3. Results

Half of our included healthy participants in the study (5 out of 10) receiving PDT treatment were female with a median age of 30 years (range 21–54 years) and a median BMI of 22.3 kg/m<sup>2</sup> (19.0–24.9 kg/m<sup>2</sup>). Demographic characteristics were similar in the control group without PDT [(7 female, median age of 30 years (range, 22–50 years), and a median BMI of 25.02 kg/m<sup>2</sup> (range, 18.6–26.8 kg/m<sup>2</sup>)].

#### 3.1. Culture results

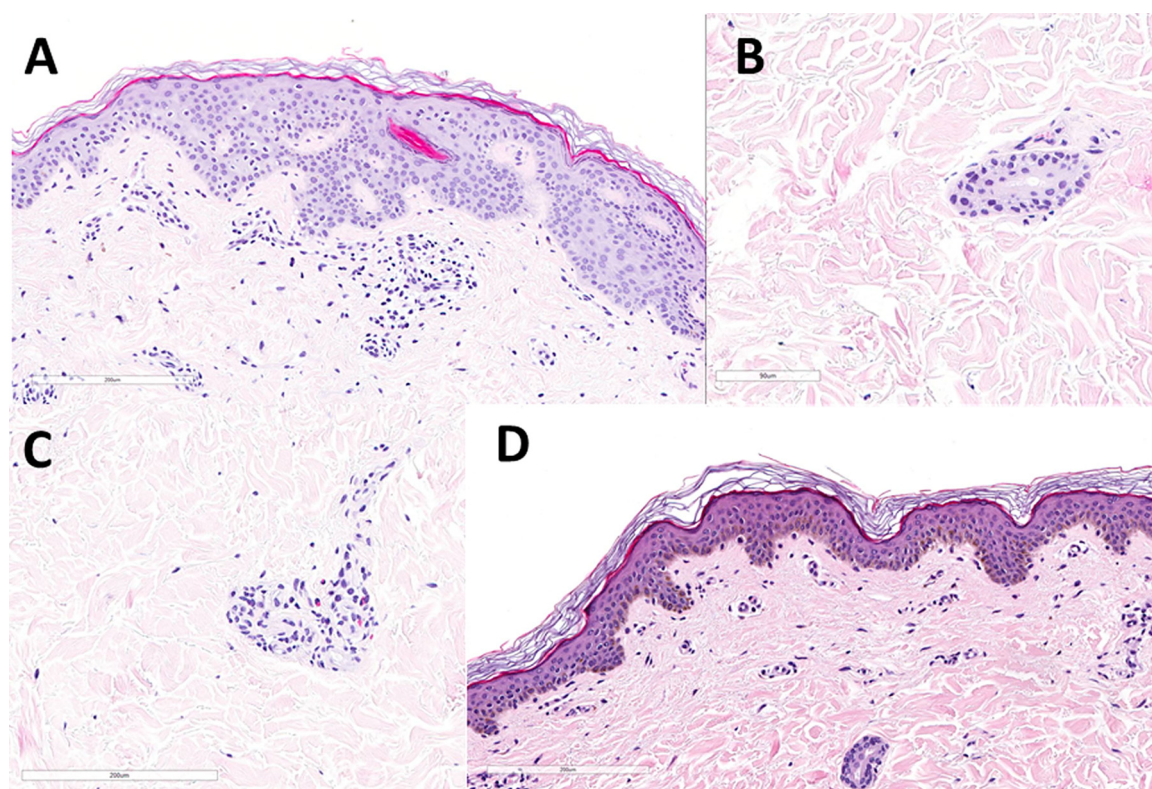
In the PDT group, all 10 participants were colonized with different bacteria such as coagulase-negative staphylococci (*Staphylococcus caprae/capitis*, *Staphylococcus epidermidis*, *Staphylococcus hominis*, *Staphylococcus warneri/pasteuri*), *C. acnes*, *Micrococcus luteus*, and others at baseline (Fig. 2A). Immediately after MAL-PDT, skin was culturally sterile in 7 (70%) participants. In the remaining 3 participants, we observed bacterial growth of *S. epidermidis*, *S. hominis* and/or *C. acnes*. After further skin antiseptis treatment, we achieved complete sterility in all 10 participants (Fig. 2A, Table 1).

The effect of MAL-PDT on skin antiseptis did not last 1 or 3 weeks post-treatment, with skin sterility after antiseptis decreasing to 62.2% and 40%, respectively. This was similar to the control group, where we obtained sterility in 50% by performing skin antiseptis treatment only (Table 1). Almost all tested bacterial species recolonized within 7–21 days in varying amounts, with *C. acnes* presenting most frequently. In addition, *Corynebacterium tuberculoearicum* was immediately detected after 7 and 21 days. Skin antiseptis reduced the amount of all recolonized bacteria but did not eradicate them completely (Fig. 2B–C). We did not perform statistical analysis due to low patient numbers and did not investigate for the presence of antibiotic resistance.

#### 3.2. Histopathology

In skin biopsies, all specimens showed slight inflammation with lymphocytes and eosinophils presenting immediately after PDT on day 0 in the perivascular compartment (n = 2) (Table 2, Fig. 3). There was no inflammation around eccrine sweat glands or around sebaceous glands. After 7 days, similar lymphocytic and eosinophilic presence was detected in the perivascular compartment in one of two participants; this participant had also inflammation with lymphocytes and eosinophils around eccrine sweat glands. Aside from inflammatory infiltrate,





**Fig. 3.** Exemplary histology images noted during PDT. A: Slight perivascular inflammation immediately after PDT (visit 0). B: Close up view of slight perieccrine inflammation 7 days after PDT. C: Close up view of slight perivascular inflammation consisting of lymphocytes and eosinophils 7 days after PDT. D: Untreated control without inflammation.

**Table 3**

Side effects during and after MAL-PDT in 10 participants.

Side effects	Nr (%) during PDT	Nr (%) after PDT
Redness Grade 1	10 (100)	10 (100)*
Skin irritation (burning, tingling)	7 (70)	5 (50)
Itching	0 (0)	3 (30)

\* up to 7 days.

no changes in the histomorphology of sweat glands or sebaceous glands could be observed. After 21 days, inflammation had completely disappeared in all participants ( $n = 4$ ). The untreated control biopsies from the left groin showed no inflammation throughout the treatment ( $n = 4$ ).

### 3.3. Side effects of PDT

PDT was generally well tolerated. Side effects (localized redness) were slight and temporary. All participants reported slight redness (Grade 1 according CTCAE V5) during and after PDT, which resolved within 7 days after the treatment (Table 3, Supplementary Figure S1). Seven out of 10 participants reported a slight sensation of burning (Grade 1–2 according CTCAE V5) during PDT, which was comforted with a cooling water spray during the treatment. Itching was only reported by 3 participants during the follow-up period but not during PDT (Table 3).

## 4. Discussion

We demonstrated that MAL-PDT in combination with standard skin antiseptic treatment completely inhibited bacterial growth of skin-colonizing bacteria in the groin area of 10 healthy participants. Skin antiseptic or PDT monotherapy achieved less sterility compared to

combination therapy with skin antiseptic. However, the effect of PDT on skin antiseptic did not last until 7 or 21 days. Recolonization was represented mostly by *S. epidermidis* and *C. acnes*, common skin commensals [21] associated with PJI [1]. Based on these results, MAL-PDT would be a promising tool when used on the day of surgery to eliminate the skin microbiome. However, using PDT with topical MAL cream led to transient skin erythema, possibly from the MAL prodrug that induces the photosensitizing agent Pp IX, which is an obstacle for immediate surgery.

Achieving 100% skin sterility with MAL-PDT and skin antiseptic treatment is an extremely promising study outcome compared to the 50% sterility witnessed using skin antiseptic treatment alone. Bryld and Jemec investigated if using PDT with MAL as a prodrug for the photosensitizer Pp IX could change the normal skin flora in patients undergoing standard PDT for skin disease treatment but reported no significant effects [22]. Compared to 5-ALA, MAL has been shown to have a more selective and deeper distribution of photoactive porphyrins in thick basal cell carcinomas [23] and sebaceous glands [19], with less systemic uptake and pain during irradiation [24]. We chose MAL (ester of 5-ALA) in combination with a red-light source at a wavelength of 633 nm to penetrate deeper into the skin layers and target eccrine glands. Skin biopsies from our participants only demonstrated slight perivascular inflammation immediately after PDT but no changes to eccrine or sebaceous glands [25]. Previous investigation by Itoh et al. described a slight decrease of nuclei of sebaceous glands. Repeated PDT sessions may therefore be necessary to successfully attack all sebaceous or eccrine glands [26].

We documented some mild side effects (local redness, burning sensation) during and after irradiation, resolving within 1 week, coordinating with previous literature [19,25,27,28]. In patients treated for acne, lesions returned to normal skin tone without hyperpigmentation after 1 month [25]. The skin redness after irradiation might be a limiting factor for surgeons concerned with proper wound

healing. However, our histological analysis of the dermis showed only a slight immediate or delayed inflammation, favoring the use of PDT and does not exclude it as a potential prevention strategy. Hence, more studies are needed to determine the optimal time point for PDT prior to surgery to achieve the maximum bactericidal effect with an acceptable local skin reaction. MAL-PDT with less irradiance intensity, reduced duration of the treatment, or other photosensitizers could be tested to minimize local erythema while maintaining the same bactericidal effect. Alternatively, a skin cream with human growth factors and cytokines has been discussed to treat phototoxicity after PDT [29]. Recently, PDT using daylight was presented as a pain free approach to treat actinic keratosis [30]. This could be advantageous over artificial light and decrease skin irritation.

Our evaluation for skin commensals was through conventional bacterial culture derived from skin swabs. This took us at a minimum 7 days until we were able to observe and identify colonies. Molecular techniques as real time PCR could facilitate the detection directly from tissue samples since its multiplexing capability allows rapid amplification of several bacteria simultaneously [31–33]. However, molecular techniques cannot distinguish between viable and non-viable bacteria, requiring the need for live culture techniques.

This pilot study is the first that examines the effect of PDT on the skin microbiome as an improved implant-associated infection prevention strategy in arthroplasty surgery. The ability to achieve 100% sterility immediately after MAL-PDT and skin antisepsis treatment is striking. However, it should be noted that our study population was small and participants were younger than the average age of patients undergoing arthroplasty surgery, hence larger studies within orthopedic wards are needed to further evaluate our study results. Since different approaches to improve skin antisepsis have been performed so far with no promising effect [4] or may lead to emergence of bacterial resistance [4,8,28], we are convinced that a strategy with an improved skin antisepsis with PDT can provide superior results to decrease PJI.

To conclude, MAL-PDT has an immediate bactericidal effect on the skin microbiome in the groin area. Due to local side effects, more clinical studies with modulation of MAL-PDT, such as decreased light exposure, shorter irradiation time, or other photosensitizers, are needed.

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## Declaration of Competing Interest

No authors have any conflict of interests.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.pdpdt.2020.101941>.

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